VOLUME 27 · NUMBER 16 · JUNE 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase 0 Clinical Trial of the Poly (ADP-Ribose) Polymerase Inhibitor ABT-888 in Patients With Advanced Malignancies

Shivaani Kummar, Robert Kinders, Martin E. Gutierrez, Larry Rubinstein, Ralph E. Parchment, Lawrence R. Phillips, Jiuping Ji, Anne Monks, Jennifer A. Low, Alice Chen, Anthony J. Murgo, Jerry Collins, Seth M. Steinberg, Helen Eliopoulos, Vincent L. Giranda, Gary Gordon, Lee Helman, Robert Wiltrout, Joseph E. Tomaszewski, and James H. Doroshow

From the Center for Cancer Research and the Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda; Laboratory of Human Toxicology and Pharmacology, Applied/Developmental Research Support Directorate, Science Applications International Corporation Frederick Inc, National Cancer Institute Frederick, Frederick; and Abbott Laboratories, Abbott Park, IL.

Submitted August 26, 2008; accepted January 13, 2009; published online ahead of print at www.jco.org on April 24, 2009.

Supported in part by federal funds from the National Cancer Institute, National Institutes of Health, under contract N01-CO-12400. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. This research was also supported by the Division of Cancer Treatment and Diagnosis and the Center for Cancer Research of the National Cancer Institute.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2007.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: James H. Doroshow, MD, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bldg. 31, Room 3A44, 31 Center Dr, National Institutes of Health, Bethesda, MD 20892; e-mail: doroshoj@mail.nih.gov.

The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2716-2705/$20.00

DOI: 10.1200/JCO.2008.19.7681

ABSTRACT

Purpose
We conducted the first phase 0 clinical trial in oncology of a therapeutic agent under the Exploratory Investigational New Drug Guidance of the US Food and Drug Administration. It was a first-in-human study of the poly (ADP-ribose) polymerase (PARP) inhibitor ABT-888 in patients with advanced malignancies.

Patients and Methods
ABT-888 was administered as a single oral dose of 10, 25, or 50 mg to determine the dose range and time course over which ABT-888 inhibits PARP activity in tumor samples and peripheral blood mononuclear cells, and to evaluate ABT-888 pharmacokinetics. Blood samples and tumor biopsies were obtained pre- and postdrug administration for evaluation of PARP activity and pharmacokinetics. A novel statistical approach was developed and utilized to study pharmacodynamic modulation as the primary end point for trials of limited sample size.

Results
Thirteen patients with advanced malignancies received the study drug; nine patients underwent paired tumor biopsies. ABT-888 demonstrated good oral bioavailability and was well tolerated. Statistically significant inhibition of poly (ADP-ribose) levels was observed in tumor biopsies and peripheral blood mononuclear cells at the 25-mg and 50-mg dose levels.

Conclusion
Within 5 months of study activation, we obtained pivotal biochemical and pharmacokinetic data that have guided the design of subsequent phase I trials of ABT-888 in combination with DNA-damaging agents. In addition to accelerating the development of ABT-888, the rapid conclusion of this trial demonstrates the feasibility of conducting proof-of-principle phase 0 trials as part of an alternative paradigm for early drug development in oncology.

J Clin Oncol 27:2705-2711. © 2009 by American Society of Clinical Oncology

INTRODUCTION

The low success rate of new molecular entities and the development of molecularly targeted agents for the treatment of cancer have necessitated re-evaluation of the standard anticancer drug development paradigm.[1] Recognizing that lack of predictive preclinical models, prolonged timelines, and high costs have hampered drug discovery, the US Food and Drug Administration developed the Exploratory Investigational New Drug (IND) Guidance to provide new regulatory pathways to enhance the drug development process.[2] Because phase 0 trials conducted under an exploratory IND involve nontoxic drug doses administered for short periods to limited numbers of patients, the preclinical toxicology data required to support the IND are less extensive; thus, these first-in-human trials, although lacking therapeutic intent, can be initiated earlier than traditional phase I studies. By providing essential pharmacodynamic (PD) and pharmacokinetic (PK) data at the initial stage of the clinical trials process, phase 0 studies can inform and expedite the subsequent development of a promising agent.[3] However, this requires validated assays and standardized tissue handling procedures for consistent results. We hypothesized that a potent, molecularly targeted modulator of chemotherapeutic efficacy would be an ideal candidate to test whether early evidence of target modulation might speed drug development.

Poly (ADP-ribose) polymerase (PARP)-1 and PARP-2 are involved in DNA repair via poly (ADP-ribosyl)ation of histones and DNA repair enzymes;

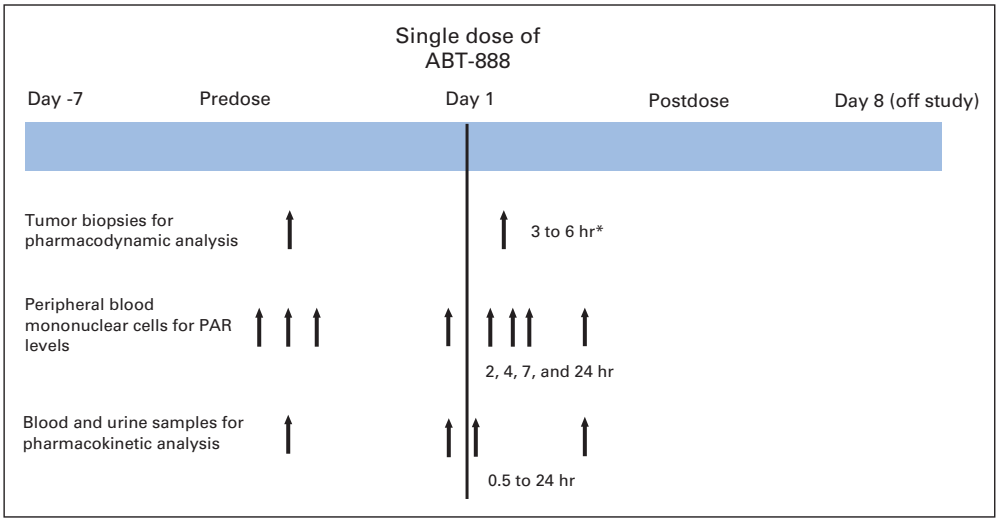

Fig 1. Schema for the phase 0 clinical study. A tumor biopsy was obtained during the week before drug administration and then 3 to 6 hours after drug administration. Blood was collected at 0.5, 1, 1.5, 2, 3, 4, 7, 12, and 24 hours; urine in 8-hour periods for 24 hours. (*) Tumor biopsies were planned once there was either significant inhibition of poly (ADP-ribose) (PAR) in peripheral blood mononuclear cells from at least one of three participants at a given dose level, or a plasma C_{max} of 0.21 μmol/L achieved in at least one participant. Patients were required to have a minimum baseline PAR level to allow post-drug biopsy. At the 50-mg dose level, three additional patients underwent a tumor biopsy 24 $\pm$ 3 hours post drug administration to evaluate the time to recovery of poly (ADP-ribose) polymerase activity.

elevated PARP levels can result in resistance to cytotoxic chemotherapy and radiation.[4-10] Thus, PARP inhibitors hold promise as chemotherapy and radiation sensitizers.[11-14] ABT-888, an orally bioavailable inhibitor of PARP, was studied because it possessed a wide margin of safety relative to its target-modulating dose in preclinical models, and demonstration of target modulation in human samples was critical to its subsequent development.[15-18]

This is the first report of a phase 0 clinical trial of a therapeutic agent in oncology with target modulation as the primary end point conducted under the Exploratory IND Guidance. Trial objectives were to determine a dose range and time course over which ABT-888 inhibited PARP activity (measured using a validated PD assay for PAR (poly [ADP-ribose], a product of PARP) in tumor and peripheral blood mononuclear cells (PBMCs), as well as the PK of ABT-888. We also developed and utilized a novel statistical approach to study PD modulation as a primary end point for trials of limited sample size.

PATIENTS AND METHODS

Eligibility Criteria

Adult patients with advanced malignancies refractory to at least one line of standard treatment were eligible, as were patients with chronic lymphocytic leukemia and follicular lymphoma if they had disease for which standard therapy was currently not indicated. Patients with primary brain tumors, brain metastases, or a history of seizures were excluded because high-dose ABT-888 caused seizures in a preclinical animal model. Prior antineoplastic therapy must have been completed at least 2 weeks before enrollment.

Consent Process

The objectives and the nontherapeutic nature of the trial were discussed in detail with potential patients, who were given ample opportunity to review and discuss the consent document with study investigators, family members, and referring physicians. Before signing the consent form, patients were asked to verbalize their understanding of the nature of the trial, and the need for tumor biopsies. This trial was conducted under a National Cancer Institute (NCI)–sponsored exploratory IND with approval from the National Institutes of Health Institutional Ethics Committee and the NCI institutional review board. Protocol design and conduct followed all applicable regulations, guidances, and local policies.

Study Design and Drug Administration

ABT-888 was supplied by the NCI Division of Cancer Treatment and Diagnosis under a collaborative agreement with Abbott Laboratories. A single oral dose of ABT-888 was administered on day 1, with serial blood sampling for PD and PK analyses performed before and after drug administration (Fig 1). Significant toxicities were defined as those considered related to ABT-888 administration and were grade $\geq$ 2 nonhematologic events or thrombocytopenia, and grade $\geq$ 3 anemia, leucopenia, or neutropenia, reported using the NCI Common Toxicity Criteria for Adverse Events version 3.0. If one patient developed significant toxicity, no additional patients could be enrolled, and the study would be put on hold.

Five dose levels, each with three patients, were planned: 10, 25, 50, 100, and 150 mg. The 10-mg starting dose was based on 1/50th of the no observed adverse effect level from a 2-week study in the most sensitive species (dog), as recommended in the Exploratory IND Guidance.[2] The objective of dose escalation was to achieve statistically and biologically significant inhibition of PAR levels at nontoxic dose levels, not to determine a maximum tolerated dose (MTD).

To minimize the possibility of performing tumor biopsies in patients receiving doses unlikely to show drug effects, biopsies were obtained once significant inhibition of PARP activity (ie, 50% reduction in PAR levels) was observed in PBMCs from at least one of the three patients at a given dose level, or a plasma C_{max} of 0.21 μmol/L (concentration associated with a significant reduction in tumor PAR levels in single-dose studies in mice) was achieved in at least one patient. All subsequent patients were then to undergo paired pre- and postdrug administration tumor biopsies (Fig 1). To proceed with sampling for PD analyses after drug administration, patients were required to have a minimum baseline PAR level (31 pg PAR per mL per 2.5×10^5 cells) to allow demonstration of a 50% reduction in PARP activity. All patients underwent blood and urine sampling for PK analyses.

PK Evaluations

Blood samples for PK analysis were at multiple time points before and within 24 hours after drug administration (Fig 1; online only Appendix). A high performance liquid chromatography-based assay with ultraviolet and mass spectrometric detection was used to measure levels of parent drug for PK analyses.[19]

PD Evaluations

Baseline and post-ABT-888 administration PAR levels were measured in PBMCs as indicated (Fig 1). Percutaneous tumor biopsies were obtained using either an 18-gauge needle under radiologic guidance (five patients) or a dermal biopsy punch (four patients; Appendix).

The PAR assay is an immunoassay with purified monoclonal antibody to PAR as the capture reagent and rabbit anti-PAR antiserum (#4336-BPC-100; Trevigen Inc, Gaithersburg, MD) as the detecting agent. Antirabbit horseradish peroxidase conjugate (#074-15-061; Kirkegaard & Perry Laboratories Inc, Gaithersburg, MD) is the chemiluminescence reporter. Assay analytic performance met validation criteria.[18]

Statistical Analyses

The trial employed a novel statistical evaluation scheme developed specifically for phase 0 trials, where the end points are PD measurements rather than toxicity.[20] Significant inhibition of PARP activity was defined as a reduction in PAR levels 3 to 6 hours after administration of ABT-888, compared to baseline, that satisfied two criteria: reduction was at least 50%, and reduction was sufficient, when compared to the variation among the baseline values, to yield 90% statistical confidence that it was not due to chance variation. Significant inhibition of PARP activity for a dose level was declared if two of three patients had significant inhibition in either PBMCs or tumor. For either end point, at each dose level there is 90% power to detect a true 80% rate of significant inhibition across patients, with a false-positive rate of .03. For PBMCs, the PAR level reduction threshold and the pooled standard deviations (SD) were based on intrapatient preadministration variability (four baseline measurements per patient), and for tumor on the interpatient preadministration variability (single baseline measurement per patient). Variability was measured on log-transformed values. For both tumor and PBMC measures, the difference between pre- and post-treatment log PAR values was compared to the threshold of 1.8 SD (from the corresponding pretreatment measures) to establish statistically significant reduction at the one-sided .10 level. It was recognized that interpatient variability being greater than intrapatient variability could make demonstration of statistically significant inhibition in tumor difficult.

RESULTS

Clinical Summary

Patient demographics are presented in Table 1. Nine paired tumor biopsies were performed, all without complications.

ABT-888 was well tolerated; no significant adverse effects were observed. One patient at the 10-mg dose level had an episode of mild dizziness and nausea relieved with food after receiving ABT-888; this patient had a history of recurrent nausea and dizziness associated with taking narcotics and had received his regular dose of narcotic around the time of ABT-888 administration. One patient at the 25-mg dose level developed mild dysgeusia for 3 days post-drug administration that was not associated with anorexia or decreased oral intake.

Table 1. Patient Demographics for the Phase 0 Trial of ABT-888

Parameter	Value
No. of patients screened	24
No. enrolled by sex	14
Male	11
Female	3
Age range of patients enrolled, years	49-74
Patients per dose level, mg	
10	3
25	3
50	8
No. who received ABT-888	13*
Median No. of prior therapies	3.5
Range	0-8
Diagnoses, No. of patients	
Carcinoid	1
Colorectal cancer	3
Small cell lung cancer	1
Low-grade lymphoma	3
Cutaneous T-cell lymphoma	3
Adenocarcinoma of the external auditory canal	1
Melanoma	1
Squamous cell carcinoma of the tongue	1
Subsequent therapy after completion of this trial	
Phase I	11
Standard of care	2

*One patient in the 50-mg cohort withdrew for personal reasons.

PK

ABT-888 was rapidly absorbed, and peak plasma levels occurred between 0.5 and 1.5 hours after dosing (Fig 2; Appendix Table A1). The target C_{max} of 0.21 μmol/L was exceeded in the first patient cohort; thus, all subsequent patients agreed to undergo paired pre- and post-treatment tumor biopsies. Clearance of ABT-888 in urine was rapid, and at the 50-mg dose level a large quantity of unchanged parent drug was recovered in the urine (average 70% in 24 hours; range 31% to 115%).

PAR Levels in Patient Tumor Samples and PBMCs

Baseline PAR levels in 11 of 13 patient PBMC samples and nine of 10 patient tumor samples were above the defined minimum to allow further sampling after drug administration. Post-drug PBMC PAR levels were compared to the day 1 sample (baseline) level collected immediately before ABT-888 administration (Figs 3A, 3B). The threshold for declaring statistically significant inhibition was calculated to be a 55% reduction in PAR in PBMCs and 95% in tumors.

Statistically significant reductions in PAR levels were observed in tumor samples from two of the three patients at the 25-mg dose (the third was near borderline with reduction corresponding to $P = .14$; one sided), and in PBMCs from both the assessable patients (Fig 3A). At the 50-mg dose, statistically significant reductions in PAR levels in tumor were observed in two of three assessable patients and in PBMCs from 4 of 6 evaluable patients. Therefore, by our statistical criteria using the binomial distribution, statistically significant reduction in PAR levels was observed for both tumor and PBMC samples at the

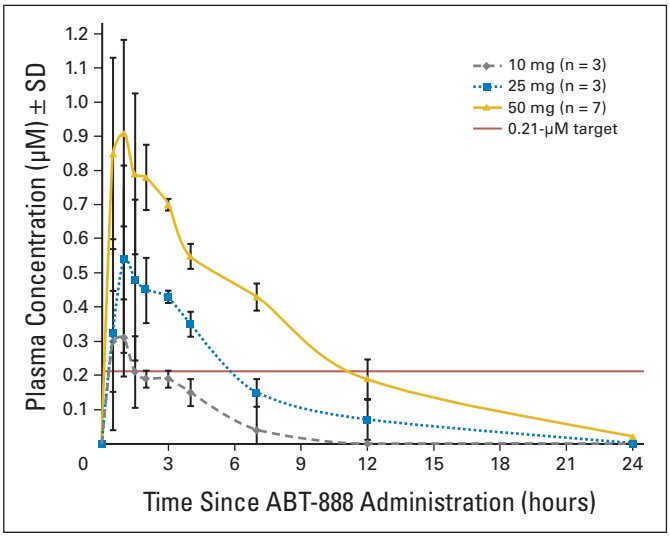

Fig 2. Average plasma concentrations (μM) of ABT-888 in patients before and after administration of a single 10-, 25-, or 50-mg dose of ABT-888 over 24 hours. Plasma C_{max} levels exceeding the target threshold of 0.21 μmol/L were achieved in all patient cohorts. Vertical bars represent standard deviations (SD).

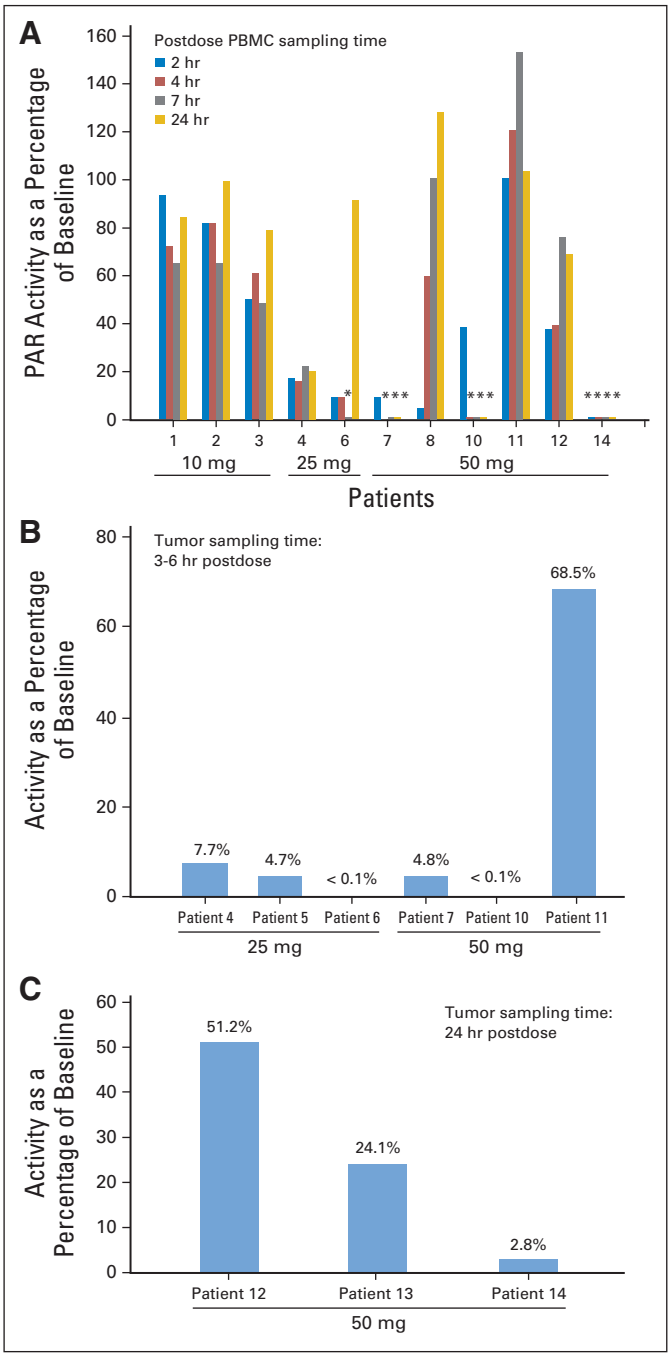

Fig 3. PAR levels in (A) peripheral blood mononuclear cells (PBMCs) and (B, C) tumor samples after administration of a single dose of ABT-888. Results are presented relative to baseline (100%). (*) Indicates the percent reduction exceeded 99% for that time point. Note: patient 5 poly (ADP-ribose) (PAR) levels were below the defined minimum at baseline; thus, no post-drug PBMC sampling was performed. PAR levels in the baseline tumor biopsy for patient 8 were below the required minimum, so this patient did not undergo a postdrug biopsy.

25-mg and 50-mg doses. By the binomial distribution, given a false-positive probability of .10 for observing significant PAR level reduction for an individual patient under the null hypothesis of no effect at that dose level, the *P* value associated with observing significant reduction in two of three patients is $P = .03$, in two of two patients is $P = .01$, and in four of six patients is $P = .001$.

Patient 11 received 50 mg of ABT-888 but had no significant reduction in PAR levels in either PBMCs or tumor (Figs 3A, 3B). PK analysis revealed plasma levels comparable to the other patients in the 50-mg cohort. Ex vivo treatment of a PBMC sample from this patient with 0.21 μmol/L (target C_{max}), or with 0.8 μmol/L ABT-888 (the patient's actual C_{max}), for 2 hours had no detectable effect on PAR levels. In comparison, PAR reduction in ex vivo PBMC samples from four healthy volunteers and from another patient at the same dose level evaluated in the same experiment was more than 90%, consistent with results from our previous studies on ex vivo PBMC sensitivity to ABT-888.[21] Comparison of this patient's samples with another study patient and three healthy donors did not identify unique single nucleotide polymorphisms (SNPs)[22] or significant differences in the ratio of PARP to poly (ADP-ribose) glycohydrolase (PARG), as measured by real-time quantitative polymerase chain reaction, that would explain these results (Appendix).

Three additional patients at the 50-mg dose level underwent a tumor biopsy at 24 ± 3 hours after ABT-888 administration to evaluate the time to recovery of PARP activity (Fig 3C). PAR levels were at least 49% below baseline levels 24 hours after drug administration, but this reduction was significant in only one of the patients.

Correlation of PAR Levels in Patient PBMC and Tumor Samples

We calculated the Pearson correlation coefficient between $\log_{10}$ reduction measures for the eight participants with PAR reduction in both PBMCs and tumor samples. The estimated correlation was relatively modest ($r = 0.51$) and did not achieve statistical significance ($P = .12$, one sided) against the null hypothesis of $r = 0$. The estimated linear regression line for $\log_{10}$ tumor PAR level reduction versus $\log_{10}$ PBMC PAR level reduction did have a slope of 1 and a constant of 0.75, indicating that PAR level reduction in PBMCs, on average, tracks PAR level reduction in tumor, but is approximately six-fold less.

For patients whose tumor biopsy PAR levels were reduced after ABT-888 administration, the Pearson correlation of PAR level reduction in PBMCs (at 4 hours) versus the ABT-888 area under the curve (AUC) was statistically significant ($r = 0.56$; $P = .05$, one sided) versus $r = 0$, but depended on the positive dose-response relationships for the two variables. It disappeared when we stratified for dose (stratified $r = -0.02$, where we correlated individual dose means rather than overall means). Tumor PAR level reduction at 3 to 6 hours did not significantly correlate with the ABT-888 AUC. Similar results were obtained when C_{max} measures were substituted for AUC measures.

DISCUSSION

In this study, we present the results of the first phase 0 clinical trial of a therapeutic agent in oncology with a PD primary end point. The trial is significant in that it provided in a short period of time both the molecular proof-of-target inhibition by ABT-888 in tumor, as well as the PK and PD data that served as the foundation for subsequent combination studies of ABT-888 with DNA-damaging agents. As shown in Figure 4, these data were available within 5 months of starting the phase 0 trial. Starting a standard phase I investigation of drug combinations based on PK and PD results from a phase 0 trial

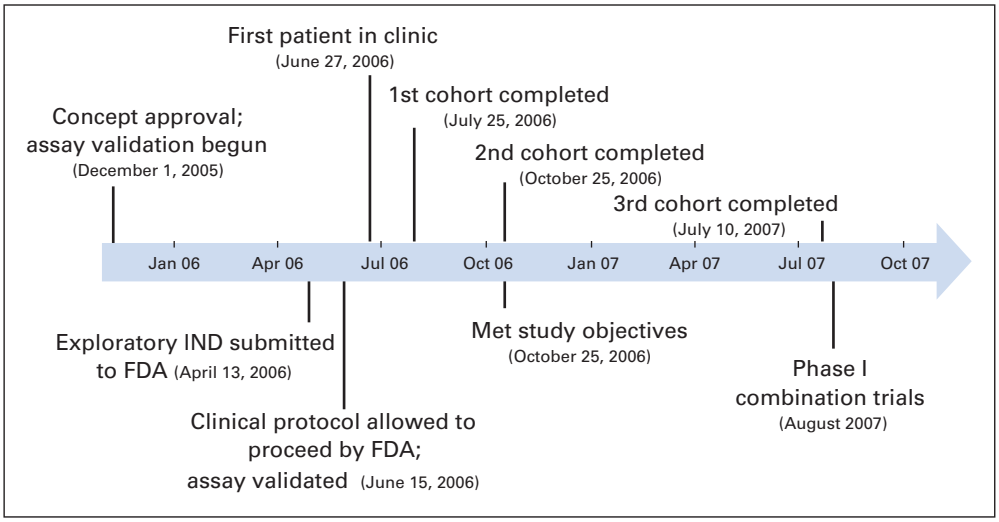

Fig 4. Timeline of the phase 0 trial of ABT-888 from clinical study concept approval by the National Cancer Institute (NCI) and Abbott Laboratories to completion. Time from accrual of the first patient on the phase 0 study to the initiation of phase I combination trials of DNA-damaging agents with ABT-888 was approximately 13 months. Note: over the past decade, for all anticancer agents for which the NCI held the Investigational New Drug Application, the median time from entry of the first patient on a first-in-human clinical trial to the initiation of phase I combination trials was approximately 30 months (N = 90 investigational agents).

without first determining the MTD of ABT-888 as a single agent is well suited to the evaluation of molecularly-targeted agents in combination with other targeted agents or cytotoxics.

Greater than 90% inhibition of PAR levels was observed 3 to 6 hours post-drug administration, with recovery at 24 hours in both xenograft models[18] and the clinical trial. This supports a twice daily schedule for ABT-888 administration in subsequent trials, ensuring adequate inhibition of PAR and optimizing the likelihood of clinical benefit. Based on the significant inhibition of PAR in tumor biopsies at 25 mg and the available capsule strengths, the recommended phase I dose of ABT-888 in combination with DNA-damaging agents is 10 mg twice a day.

Phase 0 studies with PD modulation as the primary end point rely on the PD assay for making decisions including dose escalation or defining effective target modulation. Therefore, the analytic performance of an assay is critical, and the assay needs to be validated before trial initiation.[18,23] The PD assay, timing of sample collection, and sample storage and handling procedures used in this trial were all based on extensive preclinical investigations specifically designed to validate assay techniques and to establish standard operating procedures.[3,18] It is important to emphasize that the rapid completion of complex, early-phase clinical trials requires an integrated, multidisciplinary research team capable of performing PK and PD studies in real time (in this trial, 48 hours or less after sample acquisition).

We observed one patient in our 50-mg dose cohort whose ABT-888 plasma C_{max} and AUC levels approximated the mean for all other patients at that dose level, but who demonstrated no decrease in PAR levels in PBMCs or tumor after drug exposure. We investigated whether a mutation in the *PARP* gene or significantly low levels of PARG could account for the lack of observed drug effect. No unique SNPs were identified, and the PARP/PARG ratio was not significantly different when compared to other patients or healthy donors. The mechanism of resistance to PARP inhibitor therapy needs to be further explored. However, our ability to accurately confirm the lack of responsiveness by treating PBMCs ex vivo with ABT-888 raises the possibility of ex vivo screening of PBMCs from patients in future trials to detect those likely to respond to ABT-888.

Tumor biopsies for research purposes are often obtained in cancer clinical trials; however, it has been argued that the perception of benefit could be influencing the acceptance of invasive procedures in such studies.[24,25] However, the consent to obtain tumor biopsies in this phase 0 trial was given with the clear understanding of the nontherapeutic nature of such a procedure.[26]

There are very few publications demonstrating the value of results from research biopsies obtained during early-phase clinical trials.[25] We suggest that it is not appropriate to ask patients for biopsy samples unless the assay procedures to be employed have been carefully validated. As demonstrated in this study, preclinical assay qualification can permit scientifically meaningful and statistically valid conclusions to be drawn from a limited number of biopsy samples. We understand that phase 0 studies may be more difficult to perform outside of the NCI because of the need for both a highly motivated patient population and substantive research resources to develop and validate the assays and obtain multiple tumor biopsies.

Using the novel statistical evaluation scheme that we developed specifically for use in phase 0 trials, we demonstrated statistically significant inhibition of PAR levels in both tumor and PBMCs after a single dose of ABT-888. The statistical correlation observed between the effects of ABT-888 in PBMCs versus tumor samples raises the possibility of using PBMCs as tumor surrogates, obviating the need for biopsies. We are evaluating this observation further in phase I ABT-888 combination trials.

The successful and expeditious conduct of this trial, and the impact it has had on the development timeline of ABT-888 (Fig 4), provide an initial example of a new paradigm for early therapeutics development in oncology. Clearly, several additional phase 0 trials will need to be completed under the Exploratory IND Guidance, and their long-term impact on improving the success rate and timeline assessed, before phase 0 trials will be considered to have an established role in the anticancer drug development process. The US Food and Drug Administration's new regulatory policy has provided an important and timely opportunity to expeditiously conduct and complete novel, proof-of-principle clinical trials of molecularly targeted therapeutic and imaging agents. The potential for a major impact of phase 0 trials and the exploratory IND on

developing new anticancer drugs provides a strong stimulus for the broader uptake and enhanced application of carefully conceived, pharmacodynamically driven early-phase clinical trials in oncology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Jennifer A. Low, Genentech Inc (C); Helen Eliopoulos, Abbott Laboratories (C); Vincent L. Giranda, Abbott Laboratories (C); Gary Gordon, Abbott Laboratories (C) **Consultant or Advisory Role:** Robert Kinders, Trevigen Inc (C), Kirkegaard & Perry Laboratories Inc (U) **Stock Ownership:** Jennifer A. Low, Genentech Inc; Helen Eliopoulos, Abbott Laboratories; Vincent L. Giranda, Abbott Laboratories; Gary Gordon, Abbott Laboratories **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Shivaani Kummar, Robert Kinders, Martin E. Gutierrez, Larry Rubinstein, Ralph E. Parchment, Jennifer A. Low, Alice Chen, Anthony J. Murgo, Jerry Collins, Seth M. Steinberg, Helen Eliopoulos, Vincent L. Giranda, Gary Gordon, Robert Wiltrout, Joseph E. Tomaszewski, James H. Doroshow
Financial support: Robert Wiltrout, James H. Doroshow
Administrative support: Ralph E. Parchment, Jiuping Ji, Lee Helman, Joseph E. Tomaszewski, James H. Doroshow
Provision of study materials or patients: Shivaani Kummar, Martin E. Gutierrez, Ralph E. Parchment, Anthony J. Murgo, Joseph E. Tomaszewski, James H. Doroshow
Collection and assembly of data: Shivaani Kummar, Robert Kinders, Ralph E. Parchment, Lawrence R. Phillips, Jiuping Ji, Anne Monks, Jennifer A. Low, Anthony J. Murgo, Joseph E. Tomaszewski, James H. Doroshow
Data analysis and interpretation: Shivaani Kummar, Robert Kinders, Larry Rubinstein, Ralph E. Parchment, Lawrence R. Phillips, Jiuping Ji, Anne Monks, Jennifer A. Low, Alice Chen, Anthony J. Murgo, Jerry Collins, Seth M. Steinberg, Joseph E. Tomaszewski, James H. Doroshow
Manuscript writing: Shivaani Kummar, Larry Rubinstein, Ralph E. Parchment, Anthony J. Murgo, Jerry Collins, Seth M. Steinberg, Robert Wiltrout, James H. Doroshow
Final approval of manuscript: Shivaani Kummar, Larry Rubinstein, Alice Chen, Anthony J. Murgo, Jerry Collins, Helen Eliopoulos, Vincent L. Giranda, Gary Gordon, James H. Doroshow

REFERENCES

1. Kola I, Landis J: Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 3:711-715, 2004
2. US Food and Drug Administration: Guidance for Industry, Investigators, and Reviewers. Rockville, MD, US Food and Drug Administration, 2006. http://www.fda.gov/cder/guidance/7086fnl.pdf
3. Kummar S, Kinders R, Rubinstein L, et al: Compressing drug development timelines in oncology using phase '0' trials. Nat Rev Cancer 7:131-139, 2007
4. Amé JC, Spenlehauer C, de Murcia G: The PARP superfamily. Bioessays 26:882-893, 2004
5. Tulin A, Chinenov Y, Spradling A: Regulation of chromatin structure and gene activity by poly (ADP-ribose) polymerases. Curr Top Dev Biol 56:55-83, 2003
6. Schreiber V, Dantzer F, Amé JC, et al: poly (ADP-ribose): Novel functions for an old molecule. Nat Rev Mol Cell Biol 7:517-528, 2006
7. Tomoda T, Kurashige T, Moriki T, et al: Enhanced expression of poly (ADP-ribose) synthetase gene in malignant lymphoma. Am J Hematol 37: 223-227, 1991
8. Shiobara M, Miyazaki M, Ito H, et al: Enhanced polyadenosine diphosphate-ribosylation in cirrhotic liver and carcinoma tissues in patients with hepatocellular carcinoma. J Gastroenterol Hepatol 16:338-344, 2001
9. Masutani M, Nozaki T, Nakamoto K, et al: The response of Parp knockout mice against DNA damaging agents. Mutat Res 462:159-166, 2000
10. de Murcia JM, Niedergang C, Trucco C, et al: Requirement of poly (ADP-ribose) polymerase in recovery from DNA damage in mice and in cells. Proc Natl Acad Sci U S A 94:7303-7307, 1997
11. Alderson T: New targets for cancer chemotherapy–poly (ADP-ribosylation) processing and polyisoprene metabolism. Biol Rev Camb Philos Soc 65:623-641, 1990
12. Jagtap P, Szabó C: poly (ADP-ribose) polymerase and the therapeutic effects of its inhibitors. Nat Rev Drug Discov 4:421-440, 2005
13. Tentori L, Graziani G: Chemopotentiation by PARP inhibitors in cancer therapy. Pharmacol Res 52:25-33, 2005
14. Plummer ER: Inhibition of poly (ADP-ribose) polymerase in cancer. Curr Opin Pharmacol 6:364-368, 2006
15. Donawho CK, Luo Y, Luo Y, et al: ABT-888, an orally active poly (ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res 13: 2728-2737, 2007
16. Albert JM, Cao C, Kim KW, et al: Inhibition of poly (ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models. Clin Cancer Res 13: 3033-3042, 2007
17. Ratnam K, Low JA: Current development of clinical inhibitors of poly (ADP-ribose) polymerase in oncology. Clin Cancer Res 13:1383-1388, 2007
18. Kinders RJ, Hollingshead M, Khin S, et al: Preclinical modeling of a phase 0 clinical trial: Qualification of a pharmacodynamic assay of poly (ADP-ribose) polymerase in tumor biopsies of mouse xenografts. Clin Cancer Res 14:6877-6885, 2008
19. Phillips LR, Hill KD, Majerova E, et al: Liquid chromatographic determination of NSC 737664 (ABT-888: an inhibitor of poly (ADP-ribose) polymerase (PARP)) in plasma and urine in a phase 0 clinical trial. J Liq Chromatogr Relat Technol 32:261-272, 2009
20. Murgo AJ, Kummar S, Rubinstein L, et al: Designing phase 0 cancer clinical trials. Clin Cancer Res 14:3675-3682, 2008
21. Ji J, Redon C, Pommier Y, et al: Poly-adeninosinediphosphate-ribose polymerase inhibitors as sensitizers for therapeutic treatments in human tumor and blood mononuclear cells. J Clin Oncol 25:613s, 2007 (suppl; abstr 14024)
22. National Center for Biotechnology Information Entrez SNP Database, dbSNP Build 129. http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp
23. Kinders R, Parchment RE, Ji J, et al: Phase 0 clinical trials in cancer drug development: From FDA guidance to clinical practice. Mol Interv 7:325-334, 2007
24. Dowlati A, Haaga J, Remick SC, et al: Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation. Clin Cancer Res 7:2971-2976, 2001
25. Helft PR, Daugherty CK: Are we taking without giving in return? The ethics of research-related biopsies and the benefits of clinical trial participation. J Clin Oncol 24:4793-4795, 2006
26. Gutierrez M, Collyar D: Patient perspectives on phase 0 clinical trials. Clin Cancer Res 14:3689-3691, 2008

Glossary Terms

PBMC (peripheral blood mononuclear cell): A single nucleus cell found circulating in the bloodstream (normally includes lymphocytes and monocytes).

SNP (single nucleotide polymorphism): Genetic polymorphisms are natural variations in the genomic DNA sequence present in greater than 1% of the population, with SNP representing DNA variations in a single nucleotide. SNPs are being widely used to better understand disease processes, thereby paving the way for genetic-based diagnostics and therapeutics.

AUC (area under the curve): A measure of the amount of drug in the blood over a set period of time (e.g., 24 hours) that can be used to determine drug exposure.

Exploratory IND: The Exploratory Investigational New Drug (IND) Guidance was developed by the FDA to provide new regulatory pathways for drug development and clinical evaluation. Clinical studies conducted under an exploratory IND involve administering small amount of an investigational agent for short periods to a limited number of subjects with no therapeutic or diagnostic intent. The results can provide essential pharmacodynamic, pharmacokinetic and/or imaging data at the initial stage of the clinical trials process to inform and expedite the subsequent development of promising new agents.

Pharmacodynamics: The study of the biochemical and physiological effects of a drug on the body.

Surrogate: A biologic marker evaluated in place of the actual marker of interest. For example, studying a marker for drug effect in blood instead of tumor. The relationship between the marker under study and the marker of interest needs to be established before using the term surrogate.

Phase 0 clinical trial: A first-in-human clinical trial conducted under an exploratory IND that has no therapeutic or diagnostic intent and involves very limited human exposure. The results of a Phase 0 trial can provide essential pharmacodynamic, pharmacokinetic and/or imaging data at the initial stage of the clinical trials process to inform and expedite the subsequent development of promising new agents.

Poly (ADP-ribose) (PAR): A negatively charged polymeric macromolecule produced by the PARP family of enzymes that is involved in a wide range of biological processes.

Poly (ADP-ribose) polymerase (PARP): The PARP family of nuclear enzymes facilitate DNA repair via poly (ADP-ribose)ylation of histones and DNA repair enzymes.

Validated assay: An assay that meets defined criteria for reproducibility, reliability, sensitivity, and accuracy.